NEW ANTIRETROVIRAL DRUGS: WHAT'S ON THE HORIZON IN 2005?

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Despite the present number of available antiretrovirals (ARVs), there continues to be a need for new medications with improved tolerability, and activity against resistant virus. This article will review three groups of ARVs: those available in North America and Europe but not yet registered in South Africa; new formulations of drugs for which the parent formulations are already available in South Africa; and promising new compounds in early clinical stages of development. Table I shows the year of approval of ARVs available for treatment of HIV-infected individuals, in both the USA and South Africa and Table II summarises the characteristics and rationale for new ARVs.

NEW NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

There are 7 compounds within this class available for therapy; however, cross-resistance, mitochondrial toxicity, overlapping side-effect profiles and the use of dual NRTIs as a backbone of many triple therapy regimens all combine to limit NRTI-therapeutic options. Members of this class under development include both new molecules and new formulations of existing approved drugs.

Tenofovir disoproxil fumarate is a diester pro-drug of the nucleotide analogue of adenosine 5´-monophosphate. It was registered in the USA in October 2001, initially for patients failing previous therapies and recently extended to use in first-line therapy.[1,2] It also has activity against hepatitis B virus. Bioavailability is improved when administered with food (40%), and it is generally well tolerated. The prolonged elimination half-life allows once-daily administration, with the major route of elimination being both renal glomerular filtration and active tubular secretion. The recommended dosage is one 300 mg tablet daily, if creatinine clearance > 50 ml/min. Co-administration with didanosine results in significantly raised didanosine levels. It is therefore recommended that the dose of co-administered didanosine be reduced from 400 mg to 250 mg per day. New data suggest that this combination should be used with caution, as it is associated with increased early virological failures and CD4 declines even in those achieving viral suppression. It has been postulated that the combination of these adenosine derivatives may be antagonistic *in vivo*. Co-administration with the protease inhibitors (PIs), atazanavir, indinavir and lopinavir also results in increased tenofovir levels and should prompt increased surveillance for renal toxicity. Atazanavir levels are decreased by tenofovir and ritonavir boosting should be used when co-administered. However, when combined with 3TC (lamivudine) or FTC (emtricitabine), tenofovir has shown antiretroviral efficacy in both

TABLE I. ANTIRETROVIRAL DRUGS REGISTERED IN THE USA AND SOUTH AFRICA, 2004

	Year of registration	
	USA	**RSA**
Nucleoside reverse transcriptase inhibitors		
Zidovudine (AZT/ZDV)	1987	1989
Didanosine (ddI)	1991	1992
Zalcitabine (ddC)	1992	1994
Stavudine (D4T)	1994	1998
Lamivudine (3TC)	1995	1996
Abacavir (ABC)	1998	2001
Enteric-coated ddI	2000	N/R
Emtricitabine (FTC)	2003	N/R
Nucleoside reverse transcriptase inhibitor		
Tenofovir (TFV)	2001	N/R
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine (NVP)	1996	1998
Delaviradine (DLV)	1997	N/R
Efavirenz (EFV)	1998	1999
Protease inhibitors		
Saquinavir (SQV)	1995	1997
Ritonavir (RTV)	1996	1997
Indinavir (IND)	1996	1996
Nelfinavir (NLF)	1997	1999
Amprenavir (AMP)	1999	2001
Lopinavir/ritonavir (LPV/r)	2000	2001
Atazanavir (ATZ)	2003	N/R
Fosamprenavir	2003	N/R
Entry inhibitor		
Enfuvirtide (T-20)	2003	N/R

N/R = not registered as of December 2004.

TABLE II. SUMMARY OF NEW ANTIRETROVIRAL DRUGS WITH RATIONALE FOR DEVELOPMENT

Drug name	Type of drug	Rationale for development	Development phase
Tenofovir	Adenosine analogue nucleotide RTI	Once daily with unique NRTI resistance profile	FDA approved, Oct 2001
FTC	Cytidine analogue NRTI	Once daily cytidine analogue	FDA approved, July 2004
Racivir	Mixture of FTC with positive enantiomer, NRTI	Potent anti-HIV effect	Phase II
SPD 754	Deoxycytidine analogue NRTI	Cytidine analogue with activity against M184V mutation	Phase III
D-D4FC	Deoxycytidine analogue NRTI	Activity against NRTI resistance strains	Phase II
Amdoxovir	Guanine analogue NRTI	Activity against NRTI resistance strains	Phase II
ddI-EC	Enteric-coated reformulation of didanosine, NRTI	Obviates antacid buffering, less GI adverse events and drug-drug interactions	FDA approved, Oct 2000
Stavudine ER	Extended-release formulation of stavudine, NRTI	Once-daily dosing	FDA approved, Dec 2002
Capravirine	Imidazole analogue NNRTI	Extended resistance profile, 2 or 3 *pol* mutations required	Phase III
TMC-125	Diaminopyrimidine NNRTI	Active against highly NNRTI resistant virus	Phase IIA
Atazanavir	Azopeptide PI	Once-daily PI with 'lipid-friendly' profile	FDA approved, June 2003
A-681799	Azopeptide PI	Extended PI resistance profile	Phase II
Fosamprenavir	Calcium phosphate ester of amprenavir, PI	Pro-drug of amprenavir with lower pill burden	FDA approved, Oct 2003
Tipranavir	Nonpeptidic PI	Extended PI resistance profile	Phase III
TMC-114	Nonpeptidic PI with bis-THF & sulfonamide isotere	Extended PI resistance profile	Phase II
T-20	36 amino acid peptide fusion inhibitor	Peptide binding to viral gp41, blocking membrane fusion	FDA approved, March 2003

antiretroviral-experienced and naïve patients. Resistance is associated with the K65R mutation, which occurs infrequently in patients receiving tenofovir. Adverse events associated with tenofovir use include asthenia, headache and gastrointestinal upset. Tenofovir has the least propensity for mitochondrial toxicity of all the currently approved NRTIs. Nephrotoxicity, particularly tubular dysfunction, is less common than reported with use of the earlier nucleotide compound adefovir.

FTC is a fluorinated cytidine analogue approved by the Food and Drug Administration (FDA) in July 2004 for use in combination therapy of adult HIV infection.[1,2] It is closely related to 3TC but has a longer elimination half-life, allowing once-daily administration. Potency and resistance profile are similar to 3TC, although it appears that the M184V mutation emerges more slowly under FTC than 3TC selective pressure. The dose of FTC is a single 200 mg capsule once a day.

Racivir is a mixture of FTC and its positive enantiomer with potent anti-HIV and anti-HBV activity. It is well tolerated and dosed once daily. In a phase I/II dosing study of 200, 400 and 600 mg o.d. in treatment-naïve volunteers, there was a rapid decline in viral load, which remained suppressed for 14 days after cessation of therapy.[3]

SPD 754 is a deoxycytidine analogue that has *in vitro* activity against HIV strains with the 3TC resistance-associated M184V mutation. SPD 754, however, has reduced activity against mutations associated with broad resistance to NRTIs (69 insertions and Q151M). The molecule is the negative enantiomer of dOTC, a mixture of both positive and negative enantiomers. The development of dOTC was discontinued because of toxicity observed in primates, which was attributed to the positive enantiomer. A 10-day phase I study of SPD 754 in treatment-naïve patients receiving one of 5 dosages showed dose-dependent antiviral activity with no development of new RT mutations.[4] SPD 754 had the least mitochondrial toxicity in a tissue culture assay when compared with 9 other NRTIs including 3TC.

D-D4FC is another deoxycytidine analogue with *in vitro* activity against NRTI-resistant HIV strains. When dosed at 200 mg once daily for 10 days *in vivo* activity was demonstrated in both treatment-naïve and treatment-experienced patients harbouring HIV mutations associated with high-level resistance to other NRTIs.[5]

Amdoxovir (DAPD) is a guanine analogue, with a potentially attractive resistance profile. *In vitro* activity has been demonstrated against HIV strains resistant to AZT and 3TC, ddI, ddC and ABC and strains with the multiple NRTI-resistant SS insertions at codons 68 and 69. Virus containing L74V and the double mutations K65R and Q151M are fully resistant to DAPD. Excretion is predominantly renal and because of its low

solubility it can precipitate in the urine. There may be a risk of obstructive nephropathy in patients with renal impairment. Study DAPD-150 is an open-label study of 300 mg and 500 mg DAPD twice daily, in heavily pretreated (median 7.7 years) individuals with a median of 3 NRTI-resistant mutations at baseline. At a 12-week interim analysis the addition of DAPD to optimised therapy achieved a 0.5 log decline in viral load in 58% of subjects, and a 1.0 log decline in 42%. There was a high rate of discontinuation from this study, however, including 5 of 18 patients developing non-sight-threatening lens opacities.[6] DAPD *in vitro* activity was enhanced 10-fold by combination with ribavirin, an inosine monophosphate dehydrogenase inhibitor.[7]

Videx EC is an enteric-coated formulation of ddI, which was approved for ARV use by the FDA in October 2001. Videx EC is taken once daily on an empty stomach, but the absence of antacid allows other medications to be taken at the same time. The removal of the calcium- and magnesium-based pH buffers results in fewer gastrointestinal side-effects. Videx EC is now the predominant formulation of ddI used in North America and Europe.

Extended-release stavudine (d4T XR) was approved for ARV use by the FDA in December 2002, and can be taken once a day. A randomised double-blind placebo-controlled trial compared d4T XR with the standard twice-daily immediate-release (IR) capsules and showed similar antiviral and immunological profiles in both arms. Discontinuations due to adverse events were similar in both.

NEW NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Currently available NNRTIs cannot be used sequentially following initial NNRTI failure because resistance to any one individual drug usually results in high-level resistance to all members of the NNRTI class. There is therefore considerable interest in second-generation NNRTIs, which have demonstrated *in vitro* activity against HIV strains with resistance to nevirapine and efavirenz. Reverse transcriptase mutations such as K103N and Y181C, conferring resistance against NNRTIs, result in substitution of large amino acids around the NNRTI-binding pocket, thereby decreasing RT-NNRTI contact. Second-generation NNRTIs molecules retain the ability to attach to the RT-NNRTI binding pocket even when the conformational three-dimensional structure is altered by the presence of these amino acids.

Capravirine is a second-generation NNRTI, which requires 2 or 3 key mutations to develop high-level resistance, in contrast to currently approved NNRTIs that have high-level resistance associated with a single mutation of the *pol* gene. In patients who had previously failed NNRTI therapy, capravirine 1 400 mg b.d. in combination with nelfinavir and 2 NRTIs was superior to either 2 100 mg of capravirine or placebo with nelfinavir and 2 NRTIs, but results did not reach statistical significance.[8] Clinical trials were suspended following the discovery that the drug caused vasculitis in dogs; development was resumed following safety assessment.

TMC-125 is a diaminopyrimidine NNRTI with potent *in vitro* activity against HIV, including clinical isolates with high-level resistance to current NNRTIs including K103N and Y181C mutations. A 1-week monotherapy study of 900 mg twice daily, in treatment-naïve subjects, produced a 2 log decline in viral load. In NNRTI-experienced patients, substitution of the existing NNRTI of the treatment regimen with TMC-125 resulted in a 1.0 log decline in viral load at 7 days.[9]

NEW PROTEASE INHIBITORS

Limited sequential use of PIs is possible because of the initially different resistance pathways associated with use of individual members of this class. However, acquisition of increasing numbers of PI mutations results in wider cross-resistance. There is therefore an ongoing need for new PIs with distinct resistance profiles and activity against highly PI-resistant HIV strains. PIs are also associated with derangements of lipid and glucose metabolism and associated changes in body morphology, which has motivated the search for more 'metabolic-friendly' PIs.

Atazanavir, approved in July 2003 for use in the USA, is an azopeptide PI with freedom from the cholesterol and triglyceride abnormalities that are associated with other members of the PI class. Oral bioavailability is variable but is improved when taken with food. There is a low pill burden and the recommended dosage is 400 mg (2 tablets) taken once daily. An I50L substitution appears to be a unique signature mutation of this PI, which is associated with increased *in vitro* susceptibility to other PIs.[10] Atazanavir is extensively hepatically metabolised and largely excreted in faeces. An increase in unconjugated bilirubin can occur which is related to serum drug level and patients' glucoronidation enzyme genotype (Gilbert's trait). Elimination half-life is 7 hours and bioavailability is increased by 70% with light meals. Atazanavir blood levels are boosted by co-administration with ritonavir, a CYP3A4 hepatic enzyme inhibitor, but the role of this combination in salvage therapy continues to be delineated. Important ARV interactions requiring ritonavir boosting of atazanavir include the NNRTIs, efavirenz and nevirapine CYP3A4 inducers, and the NRTI tenofovir. Dual PI combination of atazanavir and saquinavir (600/1 200 mg q.d.) in combination with 2 NRTIs has been explored but was not inferior to ritonavir and saquinavir (400/400 mg q.d.). Once-daily dosing and a benign metabolic profile make this an attractive first-line PI, particularly in those with increased cardiovascular risk factors.

A-681799 is structurally related to atazanavir with *in vitro* activity against lopinavir-resistant virus.[11] Pharmacokinetic studies indicate that ritonavir boosting is necessary.

Fosamprenavir is a calcium phosphate ester pro-drug of amprenavir, approved for ARV use in the USA in October 2003. It is almost completely hydrolysed to amprenavir and

phosphate by cellular phosphatases in the gut epithelium. It is formulated in 476 mg tablets with a side-effect profile that is similar to the parent drug. The adult dosage of 3 - 4 tablets twice daily results in a considerably decreased pill burden compared with amprenavir (16 tablets). Once-a-day dosing is possible if fosamprenavir is combined with ritonavir.[12] Unboosted fosamprenavir is associated with moderate elevations of total cholesterol but an increased HDL component.

Tipranavir is a non-peptidic HIV PI, with interest in the compound driven by *in vitro* data indicating that it has activity against strains of HIV that are multiply resistant to other current PIs. The dosing and formulation have been problematic and therapeutic boosting with ritonavir is necessary. The BI 1182.52 study of 3 doses of tipranavir/ritonavir (500/100 mg, 500/200 mg and 750/200 mg) in 216 heavily pretreated patients, with at least one PI resistance-associated mutation at baseline (not > 1 of 82L/T, 84V or 90M), achieved target plasma concentrations of tipranavir in 77% of the medium- and high-dose groups. A 1.0 log reduction in viral load was seen in those receiving the 2 higher dosages; however, the medium dose (500/100 mg) was safer and better tolerated.[13] The presence of > 2 PI resistance-associated mutations at baseline resulted in loss of tipranavir efficacy. Currently the 500/100 mg dosage has been selected for phase III development. Resist 1, an ongoing study of 620 heavily pretreated patients (median 12 ARVs), demonstrated that tipranavir had significant activity against highly resistant virus but outcomes were improved when used with another novel agent such as T-20.

TMC-114 has potent *in vitro* and *in vivo* activity against PI-resistant strains. The compound is mainly metabolised by the CYP3A4 hepatic enzyme system and is co-administered with ritonavir. A phase I/II study of 3 regimens of TMC-114 with ritonavir (300/100 mg b.i.d., 600/100 mg b.i.d. and 900/100 mg q.d.) substituted for a currently failing PI in heavily pretreated patients showed between 1.2 and 1.5 log decrease in viral load at 14 days.[14] The most commonly reported adverse events were mild to moderate gastrointestinal and CNS-related effects.

HIV ENTRY INHIBITION

HIV infection of uninfected human cells is an active process requiring complex interactions between both viral and human cellular receptors, necessary before fusion of viral and cellular membranes. There are at least three components of this process: viral-cell attachment; chemokine co-receptor attachment; and gp41 conformational change resulting in fusion of viral and target cell membranes. There is considerable clinical experience with the fusion inhibitor (T-20), which was registered for use in USA and Europe in 2003. T-20 or enfuvirtide is a 36 amino acid peptide, which inhibits HIV fusion with T-cells and thereby inhibits cellular infection.[15] The molecule acts extracellularly at nanomolar concentrations. Membrane fusion results from the interaction between two heptad repeat regions (HR1 and HR2) of gp41, which triggers a contraction of gp41 drawing the two membranes together. T-20 protein binds to HRI, thereby blocking its interaction with HR2. Mutations in the HR1 region of gp41 can result in resistance to T-20; however, there is no evidence of cross-resistance to other ARVs including the newer fusion inhibitors under development. The usual dosage of T-20 is 90 mg (1 ml) administered by subcutaneous injection twice daily, and it should be augmented with other potent drugs. The formulation is a lyophilised powder, which is dissolved in sterile water before use. The reconstituted solution should be refrigerated and used within 24 hours. Irritation at the injection site is the commonest adverse event and hypersensitivity reactions are rare. An increase in bacterial pneumonia was observed in trial patients receiving T-20 compared with those receiving placebo, but the cause is uncertain. T-20 has a role in salvage therapy of heavily pretreated individuals, but its manufacture is complex, requiring multiple steps, and it is likely to remain a costly drug.

SUMMARY

ARV therapy remains a rapidly evolving field allowing prolonged survival of our patients. Chronic management not only requires potent antiviral effect but also less demanding and less toxic regimens. The number of new compounds in the production pipeline and the increase in drug targets will increase our ability to fight this highly mutable virus.

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